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Term: 7-(2-formyl-3-hydroxyphenoxy)heptanoic acid and vaccin$

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USPT,PGPB,JPAB,EPAB,DWPI,TDBD	7-(2-formyl-3-hydroxyphenoxy)heptanoic acid and vaccin$	1	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	5-(2-formyl-3-hydroxyphenoxy)pentanamide and vaccin$	1	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	(tucaresol or 4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid) and vaccin$	8	L1

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                Index
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NEWS 17 Oct 22  Over 1 million reactions added to CASREACT
NEWS 18 Oct 22  DGENE GETSIM has been improved
NEWS 19 Oct 29  AASD no longer available
NEWS 20 Nov 19  New Search Capabilities  USPATFULL and USPAT2
NEWS 21 Nov 19  TOXCENTER(SM) - new toxicology file now available on STN
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NEWS 23 Nov 29  DWPI revisions to NTIS and US Provisional Numbers
NEWS 24 Nov 30  Files VETU and VETB to have open access
NEWS 25 Dec 10  WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
NEWS 26 Dec 10  DGENE BLAST Homology Search
NEWS 27 Dec 17  WELDASEARCH now available on STN
NEWS 28 Dec 17  STANDARDS now available on STN
NEWS 29 Dec 17  New fields for DPCI
NEWS 30 Dec 19  CAS Roles modified
NEWS 31 Dec 19  1907-1946 data and page images added to CA and CAplus

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=> s 4 (2-formyl-3-hydroxyphenoxymethyl)benzoic acid? or turcaresol
MISSING OPERATOR '4 (2-FORMYL-3'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s tucaresol or 4 (2 formyl 3 hydroxyphenoxymethyl)benzoic acid?
MISSING OPERATOR '4 (2'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s tucaresol or 4 (2 formyl 3 hydroxyphenoxymethyl) benzoic acid?
MISSING OPERATOR '4 (2'
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nested terms that are not separated by a logical operator.

=> s tucaresol
L1        64 TUCARESOL

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2        40 DUP REM L1 (24 DUPLICATES REMOVED)

=> d bib abs 1-
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L2  ANSWER 1 OF 40  BIOSIS  COPYRIGHT 2001 BIOSIS
AN  2001:262548  BIOSIS
DN  PREV200100262548
TI  Schiff base-forming compounds inhibit estrogen receptor-positive and
    -negative mammary carcinoma cell proliferation.
AU  Davis, Barbara A. (1)
CS  (1) Molecular Nutrition Laboratory, Virginia Polytechnic Institute and
    State University, Blacksburg, VA, 24061 USA
SO  FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A963. print.
    Meeting Info.: Annual Meeting of the Federation of American Societies for
    Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA
    March 31-April 04, 2001
    ISSN: 0892-6638.
DT  Conference
LA  English
SL  English
AB  Vitamin B6, in the form of pyridoxal (PL), inhibits growth of both
    estrogen receptor-positive (ER+) and -negative (ER-) mammary carcinoma
    cells in vitro. In the experiments described here,  ***Tucaresol***
    (TUC), a Schiff base-forming benzaldehyde, was used along side PL to
    compare the growth inhibitory properties of these two compounds. T-47D
    (ER+) and MDA-MB-231 (ER-) cells were cultured in phenol red-free medium
    plus vehicle control, 100 muM TUC, 300 muM TUC, 100 muM PL or 300 muM PL
    for 3d. At the 100 muM dose, TUC and PL inhibited (3H)-thymidine
    incorporation into DNA of cells similarly (52 and 58.6% of control cells,
    respectively). However at the 300 muM dose, TUC was more potent than PL,
    inhibiting (3H)-thymidine incorporation to 3% vs. 23% of control cells,
    respectively. TUC is an orally bioavailable, systemic immunopotentiating
    drug known to form a Schiff base with amines on the surface of T helper
    lymphocytes. It has been shown to inhibit colon adenocarcinoma and
    melanoma growth in vivo, presumably via its immunopotentiating properties.
    Data presented here suggest that TUC may inhibit cancer cell growth by a
    more direct mechanism, since only mammary carcinoma cells were present in
    our culture system. Further study of the Schiff base-forming compounds,
    vitamin B6 and TUC, will enhance our understanding of the mechanism by
    which they inhibit mammary carcinoma cell growth and may lead to
    identification of novel therapeutic agents.

L2  ANSWER 2 OF 40  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AN  2001376614  EMBASE
TI  Erythrocyte-active agents and treatment of sickle cell disease.
AU  Brugnara C.; De Franceschi L.; Beuzard Y.
CS  Dr. C. Brugnara, Department of Laboratory Medicine, Children's Hospital,
    300 Longwood Ave, Boston, MA 02115, United States
SO  Seminars in Hematology, (2001) 38/4 (324-332).
    Refs: 118
    ISSN: 0037-1963  CODEN: SEHEA3
CY  United States
DT  Journal; General Review
FS  025  Hematology
    030  Pharmacology
    037  Drug Literature Index
LA  English
SL  English
AB  The sickle hemoglobin (HbS)-containing erythrocyte and its membrane
    represent a logical target for sickle cell disease therapy. Several
    antisickling agents which interfere with HbS polymerization have been
    studied over the last 30 years, but none has overcome the challenge of
    delivering high concentrations inside the sickle red blood cell without
    toxicity. The sickle erythrocyte membrane has also been targeted for
    therapeutic developments. Prevention of sickle cell dehydration by use of
    specific blockers of ion transport pathways mediating potassium loss from
    the sickle erythrocyte has been shown to be a feasible strategy in vitro,
    in vivo in transgenic sickle mice, and in patients. Other approaches have
    focused on improving the hemorheology of sickle erythrocytes and reducing
    their abnormal adhesion to endothelial cells. These potential treatments
    could be used alone or in combination with other approved therapies, such
    as hydroxyurea. .COPYRGT. 2001 by W.B. Saunders Company.

L2  ANSWER 3 OF 40  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN  2001362418  EMBASE
TI  Schiff base-mediated co-stimulation primes the T-cell-receptor-dependent
    calcium signalling pathway in CD4 T cells.
AU  Hall S.R.; Rhodes J.
CS  Dr. S.R. Hall, Building 6, GlaxoSmithKline Res. and Development, Medicines
    Research Centre, Stevenage SG1 2NY, United Kingdom. srh18219@gsk.com
SO  Immunology, (2001) 104/1 (50-57).
    Refs: 27
    ISSN: 0019-2805  CODEN: IMMUAM
CY  United Kingdom
DT  Journal; Article
FS  026  Immunology, Serology and Transplantation
    029  Clinical Biochemistry
    037  Drug Literature Index
LA  English
SL  English
AB  In addition to macromolecular interactions that provide co-stimulation
    during antigen-presenting cell (APC) and CD4(+) T-cell conjugation,
    covalent chemical events between specialized ligands have been implicated
    in T-cell co-stimulation. These take the form of transient Schiff base
    formation between carbonyls and amines expressed on APC and T-cell
    surfaces. Small Schiff base-forming molecules, such as  ***tucaresol***
    , can substitute for the physiological donor of carbonyl groups and
    provide co-stimulation to T cells, thereby functioning as orally active
    immunopotentiatory drugs. The Schiff base co-stimulatory pathway in T
    cells has been partially characterized in terms of changes in Na(+) and
    K(+) transport, and activation of the mitogen activated protein kinase
    (MAPK) ERK2. In the present study, the effects of Schiff base
    co-stimulation by  ***tucaresol***  on the T-cell receptor
    (TCR)-dependent pathway leading to Ca(2+) release were investigated.
    Schiff base co-stimulation by  ***tucaresol***  was found to prime for
    enhanced TCR-dependent phospholipase C-.gamma. phosphorylation, inositol
    1,4,5-triphosphate production, and Ca(2+) mobilization that correlated
    with functional enhancement of interleukin-2 production in primary T
    cells. The effects on Ca(2+) occurred comparably in Jurkat and primary
    CD4(+) T cells responding to anti-CD3 monoclonal antibody. Enhancement of
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the Ca(2+) response required a 10-min priming period and was prevented by prior covalent ligation of cell-surface free amino groups by sulpho-N-hydroxy succinimido-biotin; clofilium-mediated inhibition of ***tucaresol*** -induced changes in intracellular K(+); and selective inhibition of the MAPK pathway. The data are consistent with a priming mechanism in which late co-stimulation-triggered events exert a positive influence on early TCR-triggered events. In additional studies of murine T cells expressing trans-gene TCRs, ***tucaresol*** was likewise shown to prime for enhanced Ca(2+) mobilization in response to physiological TCR-engagement by MHC-peptide complexes.

L2 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 2000:725478 CAPLUS
DN 133:291106
TI Immunomodulating polymers
IN Tzianabos, Arthur O.; Kasper, Dennis L.; Onderdonk, Andrew B.; Wang, Ying
PA Brigham and Women's Hospital, Inc., USA
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000059515	A2	20001012	WO 2000-US8586	20000331
WO 2000059515	A3	20010111		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-127584 P 19990402
US 1999-162457 P 19991029
AB Methods and products for inducing IL-2 secretion, inducing IL-10 secretion, activating T cells, suppressing IgG antibody response to specific antigen, promoting allograft survival, reducing postoperative surgical adhesion formation, and protecting against abscess formation assocd. with surgery, trauma or diseases that predispose the host to abscess formation are provided. The methods of the invention are accomplished using an immunomodulator which is a polymer having at least two repeating charge motifs sepd. by at least a certain min. distance.

L2 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 2000:161160 CAPLUS
DN 132:199039
TI Method of DNA vaccination
IN Charo, Jehad; Kiessling, Rolf
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000012121	A1	20000309	WO 1999-EP6217	19990825

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9957402	A1	20000321	AU 1999-57402	19990825
EP 1107785	A1	20010620	EP 1999-944505	19990825

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

NO 2001000922	A	20010423	NO 2001-922	20010223

PRAI GB 1998-18627 A 19980826
WO 1999-EP6217 W 19990825
AB A method of vaccinating a mammal against a disease state, comprising administrating to said mammal, within an appropriate vector, a nucleotide sequence encoding an antigenic peptide assocd. with the disease state; addnl. administering to said mammal a compd. which enhances both humoral and cellular immune responses initiated by the antigenic peptide, the compd. being selected from the list contained herein, wherein the compd. is preferably ***Tucaresol*** or a physiol. acceptable salt or ester thereof, where appropriate.
RE.CNT 5
RE
(1) Rhodes, J; IMMUNOLOGY TODAY 1998, V17(9), P436 CAPLUS
(2) Rhodes, J; NATURE 1995
(3) Sasaki, S; CLINICAL AND EXPERIMENTAL IMMUNOLOGY 1998, V111, P30 CAPLUS
(4) Sasaki, S; INFECTION AND IMMUNITY 1998, V66(2), P823 CAPLUS
(5) Wellcome Found; WO 9407479 A 1994 CAPLUS

L2 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 2000:891632 CAPLUS
DN 134:41090
TI Peptide immunogen as vaccine for allergic reaction and its preparation
IN Liu, Qingliang
PA Shanghai Inst. of Biological Products, Ministry of Health, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 30 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1253953	A	20000524	CN 1998-121989	19981112

AB Human IgE receptor-binding peptide epitopes are disclosed for use as vaccines for treating hypersensitivity. The peptides are conjugated with carrier protein, or are fusion protein contg. carrier protein, and are administered with adjuvant. The carrier protein is selected from hepatitis B surface antigen, hepatitis B core antigen, or nucleoprotein of rabies virus, preferably hepatitis B surface antigen. The adjuvant is liposome, Al(OH)3 gel, gamma-inulin, or ***tucaresol*** , preferably liposome. The human vaccine is prepd. by synthesizing and purifying peptide immunogen, conjugated with carrier protein in the presence of chem. crosslinking agent (or transferring into E. coli, saccharomyces, or phage, expressing, sepg.), and mixing with adjuvant. The chem. crosslinking agent is glutaraldehyde, bis(diazo)benzidine, etc.

L2 ANSWER 7 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
AN 2000196781 EMBASE
TI Activity of the novel immunomodulatory compound ***tucaresol*** against experimental visceral Leishmaniasis.
AU Smith A.C.; Yardley V.; Rhodes J.; Croft S.L.
CS S.L. Croft, Dept. of Infect. and Tropical Dis., London Sch. of Hygiene/Tropical Med., Keppel Street, London WC1E 7HT, United Kingdom. simon.croft@lshtm.ac.uk
SO Antimicrobial Agents and Chemotherapy, (2000) 44/6 (1494-1498).
Refs: 39
ISSN: 0066-4804 CODEN: AMACCQ
CY United States
DT Journal; Article
FS 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB ***Tucaresol*** , a novel immunomodulator, was inactive against Leishmania donovani amastigotes in both peritoneal and bone marrow macrophages in vitro at concentrations between 100 and 1 .mu.M, with toxicity to macrophages and parasites at 300 .mu.M. However, against L. donovani in BALB/c mice at doses between 80 and 1.25 mg/kg of body weight administered once daily by the oral route during days 7 to 11 of infection, an optimal dose of 5 mg/kg produced a 43.8 to 62.4% suppression of liver amastigotes, with significantly reduced activity at the extremes of the dose range. This response was not related to levels of infection. No interaction with the standard pentavalent antimonial sodium stibogluconate (Pentostam) was observed during this period of infection. The optimum dose of 5 mg/kg was ineffective when administered during the first week of infection and was most effective against the liver infection when administered during weeks 2 to 3 of infection (42.3 to 46.8% inhibition) and against the splenic infection when administered during week 6 of infection (59.5% inhibition). The optimum dose of ***tucaresol*** against L. donovani in C57BL/6 mice was 5 mg/kg, which produced a 40.8 to 48.7% suppression of liver amastigotes when administered in a range of 80 to 1.25 mg/kg during days 7 to 11 of infection. The drug had no activity against L. donovani infections in C.B-17 scid mice when the same regimen was used.

L2 ANSWER 8 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
AN 2000436813 EMBASE
TI In vitro immunomodulatory properties of ***tucaresol*** in HIV infection.
AU Clerici M.; Cogliati M.; Rizzardini G.; Colombo F.; Fossati S.; Rhodes J.; Bray D.; Piconi S.
CS M. Clerici, DiSP LITA Vialba, Via G.B. Grassi, 74, 20154 Milano, Italy. mago@mailserver.unimi.it
SO Clinical Immunology, (2000) 97/3 (211-220).
Refs: 32
ISSN: 1521-6616 CODEN: CLIIFY
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB The immunomodulatory properties of ***tucaresol*** (compound 589C80) were tested on in vitro antigen- and mitogen-stimulated proliferation and cytokine production by peripheral blood mononuclear cells (PBMC) of HIV-infected individuals and healthy controls (HC). Results showed that ***tucaresol*** : (1) increases influenza A virus-, gp 160 peptide-, and HLA alloantigen-stimulated proliferation as well as interleukin (IL)-2 and interferon gamma (IFN.gamma.) production by PBMC of HIV-infected individuals with higher CD4 counts (>500/.mu.l) but had only a marginal immunomodulatory effect on PBMC of patients with lower CD4 counts (<500/.mu.l); (2) did not modify IL-10 production; (3) augmented CD25 expression on mitogen-stimulated T cells of HC but not of HIV-infected individuals; and (4) marginally increased CTL activity. The immunomodulatory properties of ***tucaresol*** were confirmed by PCR analyses; additional data showed that ***tucaresol*** costimulated CD3-dependent triggering of T cells and that this stimulation was independent of CD28 costimulation. The immunomodulatory effects of ***tucaresol*** on T cell functions are characterized by a bell-shaped dose response curve; the action of the compound is optimal in the 100 to 300.mu.M range. Analyses of mitogen-stimulated apoptosis demonstrated that the lack of effect of ***tucaresol*** at higher doses is not the result of increased cell death, suggesting a role of functional impairment. These data confirm that ***tucaresol*** can stimulate T helper cell function and enhance the production of type 1 cytokines, thus eliciting cell-mediated immunity, and warrant its potential utility in the therapy of HIV infection. (C) 2000 Academic Press.

L2 ANSWER 9 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:499965 BIOSIS
DN PREV200000500086
TI Activity of the Schiff-base-forming compound ***tucaresol*** against experimental visceral leishmaniasis.
AU Croft, S. L. (1); Smith, A. C. (1); Yardley, V. (1); Rhodes, J.
CS (1) London Sch. of Hygiene and Tropical Med., London UK
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (1999) Vol. 39, pp. 730. cd-rom.
Meeting Info.: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy San Francisco, California, USA September 26-29, 1999 American Society for Microbiology
DT Conference
LA English
SL English

L2 ANSWER 10 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001082191 EMBASE
TI Overview of HBV therapy.

AU Pessoa M.G.; Wright T.L.
CS M.G. Pessoa, Dept. of Vet. Affairs Med. Center, 4150 Clement Street, San Francisco, CA 94121, United States
SO Advances in Experimental Medicine and Biology, (1999) 458/- (1-10).
Refs: 31
ISSN: 0065-2598 CODEN: AEMBAP
CY United States
DT Journal; Conference Article
FS 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English

L2 ANSWER 11 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
AN 1999044283 EMBASE
TI Development and optimisation of a generic micellar electrokinetic capillary chromatography method to support analysis of a wide range of pharmaceuticals and excipients.
AU Altria K.D.; McLean R.
CS K.D. Altria, Pharmaceutical Dev. Europe, GlaxoWellcome R and D, Ware, Hertfordshire SG12 0DP, United Kingdom. kda8029@ggr.co.uk
SO Journal of Pharmaceutical and Biomedical Analysis, (1998) 18/4-5 (807-813).
Refs: 5
ISSN: 0731-7085 CODEN: JPBADA
PUI S 0731-7085(98)00219-2
CY Netherlands
DT Journal; Article
FS 037 Drug Literature Index
LA English
SL English
AB A micellar electrokinetic capillary chromatography (MECC) method has been developed and validated to allow the analysis of a wide range of water soluble and insoluble acidic, basic and neutral drugs and excipients. An electronic database has been established to demonstrate the wide applicability of the method. The method has been validated and is now in routine use. In particular, acceptable injection precision is obtained through use of internal standards. Optimal sensitivity was obtained by using low UV wavelength detection. The method allows a number of cost and time saving benefits. Copyright (C) 1998 Elsevier Science B.V.

L2 ANSWER 12 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:119864 BIOSIS
DN PREV199900119864
TI Antileishmanial activity of the Schiff-base-forming compound ***tucaresol*** .
AU Croft, S. L. (1); Smith, A. (1); Rock, P. (1); Yardley, V. (1); Rhodes, J.
CS (1) Dep. Infect. Tropical Dis., London Sch. Hygiene Tropical Med., Keppel St., London W1E 7HT UK
SO Memorias do Instituto Oswaldo Cruz, (Nov., 1998) Vol. 93, No. SUPPL. 2, pp. 295.
Meeting Info.: XXV Annual Meeting on Basic Research in Chagas Disease and the XIV Meeting of Brazilian Society of Protozoology Caxambu, Brazil November 11-13, 1998
ISSN: 0074-0276.
DT Conference
LA English

L2 ANSWER 13 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
AN 1998224783 EMBASE
TI Effect of food and gender on the pharmacokinetics of ***tucaresol*** in healthy volunteers.
AU Peck R.W.; Wootton R.; Wiggs R.; Layton G.; Posner J.
CS Dr. R.W. Peck, Glaxo Wellcome R and D Ltd, Greenford Rd, Greenford, Middlesex UB6 0HE, United Kingdom
SO British Journal of Clinical Pharmacology, (1998) 46/1 (83-86).
Refs: 7
ISSN: 0306-5251 CODEN: BCPHBM
CY United Kingdom
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Aims: The potential effects of food and gender on the pharmacokinetics of ***tucaresol*** were investigated in healthy volunteers. Methods: Ten males (mean weight 76.5 kg, age 27-42 years) and eight females (mean weight 58.9 kg, age 18-44 years) received a single oral dose of 200 mg ***tucaresol*** on two occasions in random order. On one occasion, ***tucaresol*** was given after an overnight fast and on the other, immediately after ingestion of a standard breakfast. Results: There were no significant differences in standard pharmacokinetic parameters between the two occasions but the rate of ***tucaresol*** absorption was faster after food intake. Female subjects had higher C(max) (ratio 1.25 with 95% CI 1.10-1.44) and AUC (ratio 1.25 with 95% CI 1.05-1.49) values than males but the differences were due to the higher body weights of the males; weight-adjusted apparent total clearance values (CL/F) were not different between genders (ratio 1.03 with 95% CI 0.87-1.21). Conclusions: Food intake and gender have no significant effect on the exposure to orally administered ***tucaresol*** .

L2 ANSWER 14 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:190344 BIOSIS
DN PREV199800190344
TI The immunopotentiatory drug ***tucaresol*** primes T-cells for enhanced calcium release in response to TCR-stimulation.
AU Hall, Simon R.; Rhodes, John R.
CS Immunol. Unit, Glaxo Wellcome Res. and Dev., Med. Res. Cent., Stevenage UK
SO Cytometry, (1998) No. SUPPL. 9, pp. 76.
Meeting Info.: XIX International Congress of the International Society for Analytical Cytology Colorado Springs, Colorado, USA February 28-March 5, 1998 International Society for Analytical Cytology
ISSN: 0196-4763.
DT Conference
LA English

L2 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 1997:706430 CAPLUS
DN 128:22686
TI Regioselective synthesis of 6-substituted 2-hydroxybenzaldehyde: efficient synthesis of the immunomodulator ***tucaresol*** and related analoges
AU Zacharie, Boulos; Attardo, Giorgio; Barriault, Nancy; Penney, Christopher
CS BioChem Therapeutic Inc., Laval, PQ, H7V 4A7, Can.
SO J. Chem. Soc., Perkin Trans. 1 (1997), (19), 2925-2929
CODEN: JCPRB4; ISSN: 0300-922X
PB Royal Society of Chemistry
DT Journal
LA English
AB Two new improved procedures have been developed for the prepn. of the immunostimulant ***tucaresol*** [4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid]. These approaches, which start from resorcinol or 2,6-dimethoxybenzaldehyde, are practical and therefore amenable to scale-up. In the case of the second approach, the multi-step synthesis reported in the literature has been reduced to three steps. Furthermore, unlike the reported method, this synthesis is versatile for the prepn. of ***tucaresol*** analogs. The method is general and applicable for the prepn. of 6-substituted 2-hydroxybenzaldehydes.

L2 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 1997:575746 CAPLUS
DN 127:261658
TI Convergence of Schiff base costimulatory signaling and TCR signaling at the level of mitogen-activated protein kinase ERK2
AU Chen, Huaqing; Hall, Simon; Heffernan, Brian; Thompson, Neil T.; Rogers, Mark V.; Rhodes, John
CS Immunology Unit, Glaxo Wellcome Medicines Research Centre, Stevenage, UK
SO J. Immunol. (1997), 159(5), 2274-2281
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Schiff base formation on specialized T cell surface amines provides a costimulatory signal to T cells through a mechanism that activates Na+ and K+ transport, substantially enhancing TCR-dependent IL-2 prodn. Schiff base-forming mols. that mimic the natural carbonyl donor potently enhance immune responses and provide the first mechanism-based, orally active immunopotentiatory agents. In the present study, costimulation by the Schiff base-forming mol. ***tucaresol*** was investigated at the level of mitogen-activated protein kinase (MAPK) in T cell lines. Both TCR-directed stimulation by anti-CD3 and Schiff base stimulation by ***tucaresol*** produced a distinct mobility shift in MAPK, characterized by direct immunoblotting of cell lysate proteins subjected to SDS-PAGE, that corresponded with increased phosphorylation. Combined TCR-CD3 and ***tucaresol*** stimulation substantially enhanced and prolonged the MAPK response, providing a biochem. basis for the costimulatory nature of the pathway utilized by Schiff base signaling. The MAPK affected was identified by immunopptn. as ERK2. Both the direct effects and the TCR signal-enhancing effects of ***tucaresol*** on MAPK activation were also demonstrated in a functional MAPK assay measuring substrate phosphorylation. Borohydride redn. of ***tucaresol*** 's Schiff base-forming carbonyl group abolished both enhancement of MAPK phosphorylation and IL-2 prodn., as did a selective inhibitor of the MAPKK, MEK1. ***Tucaresol*** had no effect on TCR-mediated rises in intracellular free Ca2+ or inositol 1,4,5-triphosphate generation, while ***tucaresol*** signaling occurred normally in the lck-deficient J.CaM1.6 T cell line, consistent with convergence of ***tucaresol*** - and TCR-induced signals downstream of early TCR-mediated events.

L2 ANSWER 17 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:232894 BIOSIS
DN PREV199799532097
TI A novel immunopotentiating agent, ***tucaresol*** : Results from a multicenter, pilot study in patients with metastatic melanoma.
AU Kirkwood, J. M. (1); Schuchter, L. M.; Donnelly, S.; Slover, L.; Whiteside, T. L.; Burnham, J. P.; Heitman, C. K.; Johnston, J. M.
CS (1) Univ. Pittsburgh Cancer Inst., Pittsburgh, PA 15213 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 402.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.
DT Conference; Abstract
LA English

L2 ANSWER 18 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7
AN 97214933 EMBASE
DN 1997214933
TI Potentiation of the immune system by Schiff base-forming drugs. Mechanism of action and therapeutic potential.
AU Chen H.; Hall S.; Zheng B.; Rhodes J.
CS Dr. J. Rhodes, Immunology Unit, Cellular Sciences Division, Glaxo Wellcome Research/Development, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom
SO BioDrugs, (1997) 7/3 (217-231).
Refs: 68
ISSN: 1173-8804 CODEN: BIDRF4
CY New Zealand
DT Journal; General Review
FS 002 Physiology
004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB CD4+ T lymphocytes, which orchestrate immune responses, receive a cognitive signal when clonally distributed receptors are occupied by peptides bound to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. The latter cells provide costimulatory or accessory signals through macromolecules such as B7.1 and B7.2, which interact with coreceptors on T cells to regulate outcomes in terms of T cell activation or specific nonresponsiveness. Complementary studies of the interactions between antigen-presenting cells and T helper cells at the chemical level have implicated Schiff base formation between specialised carbonyls and amines, constitutively expressed on the surfaces of antigen-presenting cells and T cells, as an essential element in specific T cell activation. Small Schiff base-forming molecules can substitute for the natural donor of carbonyl groups and provide a costimulatory signal to the T cell. From this class of Schiff base-forming

costimulatory molecules, the small xenobiotic substituted benzaldehyde, ***tucaresol*** , has been selected for development and testing as an immunopotentiatory drug. ***Tucaresol*** , which is orally bioavailable available and systemically active, enhances CD4+ T helper cell and CD8+ cytotoxic T cell responses in vivo, and selectively favours a T helper 1 profile of cytokine production. In murine models of virus infection and syngeneic tumour growth it has substantial therapeutic activity. Schiff base formation by ***tucaresol*** on T cell surface amines provides a costimulatory signal to the T cell through a mechanism that activates clofilium-sensitive K+ and Na+ transport. The pathway utilised by ***tucaresol*** converges with T cell receptor signalling at the level of mitogen-activated protein (MAP) kinase, promoting the activation of MAP kinase kinase (MEK) and consequential tyrosyl phosphorylation of ERK2. ***Tucaresol*** is the first orally active, mechanism-based immunopotentiatory drug available for therapeutic testing. It is currently undergoing phase I/II clinical trials in chronic hepatitis B virus infection, HIV infection and malignant melanoma.

L2 ANSWER 19 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:330034 BIOSIS
DN PREV199799629237
TI Beneficial in vitro effects of ***tucaresol*** on the immune response to hepatitis C virus.
AU Cramp, M. E. (1); Chokshi, S.; Tzampouras, N.; Torre, F.; Williams, Roger; Naoumov, N. V.
CS (1) Inst. Liver Studies, King's Coll. Hosp., London UK
SO Journal of Hepatology, (1997) Vol. 26, No. SUPPL. 1, pp. 113. Meeting Info.: 32nd Annual Meeting of the European Association for the Study of Liver London, England, UK April 9-12, 1997 ISSN: 0168-8278.
DT Conference; Abstract
LA English

L2 ANSWER 20 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:240198 BIOSIS
DN PREV199799539401
TI Beneficial in vitro effects of ***tucaresol*** on the immune response to hepatitis C virus.
AU Cramp, M. E. (1); Chokshi, S.; Tzamppouras, N.; Torre, F.; Williams, Roger; Naoumov, N. V.
CS (1) Inst. Liver Studies, King's Coll. Hosp., London UK
SO Gut, (1997) Vol. 40, No. SUPPL. 1, pp. A30. Meeting Info.: Meeting of the British Society of Gastroenterology Brighton, England, UK March 18-21, 1997 ISSN: 0017-5749.
DT Conference; Abstract
LA English

L2 ANSWER 21 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8
AN 96191872 EMBASE
DN 1996191872
TI ***Tucaresol*** increases oxygen affinity and reduces haemolysis in subjects with sickle cell anaemia.
AU Arya R.; Rolan P.E.; Wootton R.; Posner J.; Bellingham A.J.
CS Dept. of Haematological Medicine, King's College School of Med./Dent., Denmark Hill,London SE5 9RS, United Kingdom
SO British Journal of Haematology, (1996) 93/4 (817-821). ISSN: 0007-1048 CODEN: BJHEAL
CY United Kingdom
DT Journal; Article
FS 025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The primary pathophysiological event in sickling is the intracellular polymerization of deoxygenated haemoglobin S. ***Tucaresol*** (589C80;4[2-formyl-3-hydroxyphenoxymethyl] benzoic acid), a substituted benzaldehyde, was designed to interact with haemoglobin to increase oxygen affinity and has been shown to inhibit sickling in vitro. We administered ***tucaresol*** to sickle cell patients in the steady state to examine the anti-sickling effect in vivo. Oral doses of ***tucaresol*** or placebo were given to nine stable sickle cell patients (aged 17-39 years; ***tucaresol*** , six; placebo, three) for 10 d. The first two patients on ***tucaresol*** were scheduled to receive a loading dose of 800 mg or 1200 mg (depending on bodyweight) for the first 4d, followed by maintenance doses of 200 or 300 mg for the next 6 d. Due to concerns over the sharp rise in haematocrit in one patient, subsequent cohorts received 300 mg ***tucaresol*** daily throughout the dosing period. The oxygen affinity of haemoglobin S was increased in all patients receiving ***tucaresol*** , with between 10% and 24% of the haemoglobin modified, dependent on dose. In all patients on ***tucaresol*** , haemolysis was reduced with rises in haemoglobin of 0.9-3.7 g/dl (mean 2.2 g/dl), falls in lactate dehydrogenase of 16-52%, and a halving of the irreversibly sickled cell counts. These effects were apparent within a few days and persisted for 1-2 weeks following discontinuation of the drug. Three of the six patients on ***tucaresol*** developed fever and cervical lymphadenopathy, with onset between days 7 and 11 from start of drug. Further evaluation of the tolerability and efficacy of ***tucaresol*** in sickle cell patients is necessary.

L2 ANSWER 22 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 9
AN 96284595 EMBASE
DN 1996284595
TI Schiff base forming drugs: Mechanisms of immune potentiation and therapeutic potential.
AU Chen H.; Rhodes J.
CS Immunology Unit, Medicine Research Centre, Glaxo Wellcome Research/Development, Gunnels Wood Road,Stevenage, Hertfordshire SG1 2NY, United Kingdom
SO Journal of Molecular Medicine, (1996) 74/9 (497-504). ISSN: 0946-2716 CODEN: JMLME8
CY Germany
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB CD4 T-lymphocytes, which orchestrate immune responses, receive a cognitive signal when clonally distributed receptors are occupied by MHC class II bound peptides on antigen-presenting cells. The latter provide costimulatory or accessory signals through macromolecules such as B7.1 and B7.2 which interact with coreceptors on T-cells to regulate outcomes in terms of T-cell activation or specific non-responsiveness. Complementary studies at the chemical level have implicated Schiff base formation between specialised carbonyls and amines, constitutively expressed on antigen-presenting cell and T-cell surfaces, as an essential element in specific T-cell activation. The small xenobiotic Schiff base forming molecule ***tucaresol*** , which substitutes for the physiological donor of carbonyl groups to provide a costimulatory signal to CD4 T-helper lymphocytes (Th-cells), has been developed for testing as an immunopotentiatory drug. ***Tucaresol*** , which is orally bioavailable and systemically active, enhances CD4 Th-cell and CD8 cytotoxic T-cell responses in vivo and selectively favours a Th1-type profile of cytokine production. In murine models of virus infection and syngeneic tumour growth it has substantial therapeutic activity. Schiff base formation by ***tucaresol*** on T-cell surface amines provides a costimulatory signal to the T-cell through a mechanism that activates clofilium-sensitive K+ and Na+ transport. The signalling pathway utilised by ***tucaresol*** converges with T-cell receptor signalling at the level of MAP kinase, promoting the tyrosyl phosphorylation of ERK2 by MEK (mitogen-activated protein kinase kinase). The Schiff base forming class of immunopotentiatory drug provides the first orally active, mechanism-based immunopotentiatory agents for therapeutic testing. ***Tucaresol*** is currently undergoing pilot phase I/II clinical trials as an immunopotentiator in chronic hepatitis B virus infection, HIV infection and malignant melanoma.

L2 ANSWER 23 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 10
AN 96256778 EMBASE
DN 1996256778
TI Covalent chemical events in immune induction: Fundamental and therapeutic aspects.
AU Rhodes J.
CS Immunology Unit, Division of Cellular Sciences, Glaxo Wellcome Medicines Res. Centre, Gunnels Wood Road,Stevenage, Hertfordshire SG1 2NY, United Kingdom
SO Immunology Today, (1996) 17/9 (436-441). ISSN: 0167-5699 CODEN: IMTOD8
CY United Kingdom
DT Journal; General Review
FS 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Costimulatory macromolecules on antigen-presenting cells and T cells play a critical regulatory role in immune induction and thus make useful immunotherapeutic targets. However, as reviewed here, by John Rhodes, studies of complementary chemical events are beginning to reveal a new level of intercellular and intracellular signalling that can be targeted by small, orally active therapeutic agents. One such molecule, ***tucaresol*** , is being developed for testing as a systemic immunopotentiatory drug.

L2 ANSWER 24 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96130491 EMBASE
DN 1996130491
TI New initiatives in combination antiretroviral chemotherapy.
AU Rooney J.F.; Warwick J.C.; Elkins M.M.; St. Clair M.H.; Barry D.W.
CS Department of Infectious Diseases, Burroughs Wellcome Co.,Research Triangle Park, NC, United States
SO Advances in Experimental Medicine and Biology, (1996) 394/- (373-382). ISSN: 0065-2598 CODEN: AEMBAP
CY United States
DT Journal; Conference Article
FS 004 Microbiology
008 Internal Medicine
030 Pharmacology
037 Drug Literature Index
LA English

L2 ANSWER 25 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11
AN 96077383 EMBASE
DN 1996077383
TI Therapeutic potential of Schiff base-forming drugs.
AU Rhodes J.
CS Immunology Unit, Research Division, Glaxo Wellcome Research/Development,Beckenham, Kent, United Kingdom
SO Expert Opinion on Investigational Drugs, (1996) 5/3 (257-268). ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Despite the sustained efforts of immunologists, drugs with which to potentiate the immune system in chronic infectious disease and cancer have remained elusive. CD4+ T helper lymphocytes, activated by antigens bound to MHC class II molecules on specialised antigen presenting cells (APCs), are an important target in any immunopotentiatory strategy because they orchestrate immune responses. In addition to presenting antigen, APCs also express surface macromolecules that provide essential co-stimulatory signals through interactions with co-receptors on T-cells. As a consequence of some of these macromolecular interactions, transient covalent chemical events occur between specialised carbonyl and amino groups to form reversible Schiff bases and this process is essential for optimal immune induction. This chemical event can be mimicked by small Schiff base-forming molecules that substitute for the natural donor of carbonyl groups and directly co-stimulate T-cells, providing a class of low-molecular weight agents that potently enhance the induction of immune responses in vivo. One such molecule, ***tucaresol*** (Glare Wellcome), has been developed for testing as an orally bioavailable, systemically active immunopotentiator drug. The formation of a Schiff base by ***tucaresol*** on specialised T-cell surface amines provides a co-stimulatory signal to the T-cell through a mechanism that activates Na+ and K+ transport. The signalling pathway initiated by ***tucaresol*** converges with T-cell receptor signalling at the level of tyrosyl phosphorylation of the MAP kinase ERK2. ***Tucaresol*** co-stimulation preferentially favours a Th1-type profile of cytokine production, enhancing the release of interleukin (IL)-2 and interferon-gamma.

(IFN.gamma.), but not IL-4 or IL-6. This may be therapeutically favourable in promoting immune responses to intracellular pathogens, such as viruses, mycobacteria and protozoal parasites, as well as responses to immunogenic tumours. The Schiff base-forming class of immunopotentiatory drug provides the first orally-active, mechanism-based immunopotentiatory agent for therapeutic testing. ***Tucaresol*** is currently undergoing pilot Phase I/II clinical trials as an immunopotentiator in chronic hepatitis B virus infection, HIV infection and malignant melanoma.

L2 ANSWER 26 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96203517 EMBASE
DN 1996203517
TI [Drepanocytosis].
RECORDAR A DREPANOCITOSE.
AU Alves M.E.; Osorio I.; Sousa Guerreiro A.
CS Internato Compl. Medicina Interna, Hospital de Pulido Valente, Alameda das Linhas de Torres, 117,1700 Lisboa, Portugal
SO Boletim do Hospital de Pulido Valente, (1996) 9/2 (95-98).
ISSN: 0870-8363 CODEN: BHPVEY
CY Portugal
DT Journal; (Short Survey)
FS 025 Hematology
037 Drug Literature Index
LA Portuguese

L2 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 1996:414959 CAPLUS
TI A simple synthesis of the immunostimulator ***tucaresol*** [4-(2-formyl-3-hydroxyphenoxymethyl) benzoic acid] and analogs
AU Zacharie, B.; Barriault, N.; Penney, C. L.; Attardo, G.
CS Immunomodulators, BioChem Therapeutic Inc., Laval, QC, H7V 4A7, Can.
SO Book of Abstracts, 212th ACS National Meeting, Orlando, FL, August 25-29 (1996), ORGN-051 Publisher: American Chemical Society, Washington, D. C. CODEN: 63BFAF
DT Conference; Meeting Abstract
LA English
AB An improved procedure was developed for the prepn. of the immunostimulant ***Tucaresol*** (1) [4-(2-formyl-3-hydroxy phenoxymethyl) benzoic acid]. Our approach, which starts from resorcinol, is practical and therefore amenable to scale-up. The multi-step synthesis reported in the literature was reduced to four steps which proceed in excellent yield. Furthermore, unlike the literature method, our synthesis is of general utility as it provides a route for the prepn. of analogs of ***tucaresol*** . Further details regarding the synthesis of ***tucaresol*** and its analogs will be presented. [Equation Omitted].

L2 ANSWER 28 OF 40 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:449039 BIOSIS
DN PREV199699171395
TI A simple synthesis of the immunostimulator ***tucaresol*** (4-(2-formyl-3-hydroxyphenoxymethyl) benzoic acid) and analogs.
AU Zacharie, B.; Barriault, N.; Penney, C. L.; Attardo, G.
CS Immunomodulators BioChem., Therapeutic Inc., 275 Armand-Frappier Blvd., Laval, PQ H7V 4A7 Canada
SO Abstracts of Papers American Chemical Society, (1996) Vol. 212, No. 1-2, pp. ORGN 51.
Meeting Info.: 212th American Chemical Society National Meeting Orlando, Florida, USA August 25-29, 1996
ISSN: 0065-7727.
DT Conference
LA English

L2 ANSWER 29 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 12
AN 95111233 EMBASE
DN 1995111233
TI Pharmacokinetics and pharmacodynamics of ***tucaresol*** , an antisickling agent, in healthy volunteers.
AU Rolan P.E.; Mercer A.J.; Wootton R.; Posner J.
CS Department of Clinical Pharmacology, Wellcome Research Laboratories, Langley Court,Beckenham, Kent BR3 3BS, United Kingdom
SO British Journal of Clinical Pharmacology, (1995) 39/4 (375-380).
ISSN: 0306-5251 CODEN: BCPHBM
CY United Kingdom
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB ***Tucaresol*** is an orally administered antisickling agent which increases the oxygen affinity of haemoglobin. The pharmacokinetics, effects on moderate graded exercise and psychometric performance of ***tucaresol*** were examined in a double-blind, placebo-controlled, parallel groups study in 12 healthy men. Three doses of ***tucaresol*** were given at 48 h intervals intended to modify 15, 25 and 32.5% of a subject's haemoglobin to a high affinity form (%MOD). Mean peak %MOD was 34%. Mean C(max) values in plasma and erythrocytes were 81.4 and 1459 .mu.g ml-1, respectively. Heart rate, compared with baseline, increased in the ***tucaresol*** group with the greatest changes at the highest %MOD and workload. There were no differences between groups in psychometric test performance. Three volunteers on active drug developed fever, rash and tender cervical lymphadenopathy with onset 7-10 days from the start of dosing, suggesting an immune mechanism. The acute increase in oxygen affinity with ***tucaresol*** is physiologically well-tolerated, but the utility of ***tucaresol*** in the management of sickle cell disease will depend on the identification of a dosing regimen with a lower incidence of drug allergy.

L2 ANSWER 30 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 13
AN 95275771 EMBASE
DN 1995275771
TI Therapeutic potentiation of the immune system by costimulatory Schiff-base-forming drugs.
AU Rhodes J.; Chen H.; Hall S.R.; Beesley J.E.; Jenkins D.C.; Collins P.; Zheng B.
CS Molecular Immunology Group, Wellcome Research Laboratories,Beckenham, Kent BR3 3BS, United Kingdom
SO Nature, (1995) 377/6544 (71-75).
ISSN: 0028-0836 CODEN: NATUAS
CY United Kingdom
DT Journal; Article
FS 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Immune responses are orchestrated by CD4 T lymphocytes, which receive a cognitive signal when clonally distributed receptors are occupied by major histocompatibility complex (MHC) class II-bound peptides on antigen-presenting cells (APCs). The APCs provide costimulatory signals, through macromolecules such as CD80, that regulate outcomes in terms of T-cell activation or anergy. We have studied essential complementary chemical events in the form of Schiff base formation between carbonyls and amines that are constitutively expressed on presenting cell and T-cell surfaces and provide a new target for manipulation of immune responses. Here we show that small Schiff base-forming molecules can substitute for the physiological donor of carbonyl groups and provide a costimulatory signal to CD4 Th-cells through a mechanism that activates clofilium-sensitive K+ and Na+ transport. One such molecule, ***tucaresol*** , enhances CD4 Th-cell responses, selectively favouring a Th1-type profile of cytokine production. In vivo ***tucaresol*** potently enhances CD4 Th-cell priming and CD8 cytotoxic T-cell priming to viral antigens, and has substantial therapeutic activity in murine models of disease.

L2 ANSWER 31 OF 40 CAPLUS COPYRIGHT 2001 ACS
AN 1994:315820 CAPLUS
DN 120:315820
TI Immunopotentiatory agents
IN Rhodes, John Richard
PA The Wellcome Foundation Ltd., UK
SO PCT Int. Appl., RCPP
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9407479	A2	19940414	WO 1993-GB2039	19930930
WO 9407479	A3	19940721		
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 609606	A1	19940810	EP 1993-307373	19930917
EP 609606	B1	19961211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
EP 678298	A2	19951025	EP 1995-110267	19930917
EP 678298	A3	19960529		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 146075	E	19961215	AT 1993-307373	19930917
ES 2096215	T3	19970301	ES 1993-307373	19930917
CN 1091005	A	19940824	CN 1993-114444	19930930
EP 614357	A1	19940914	EP 1993-921034	19930930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07002660	A2	19950106	JP 1993-277300	19930930
JP 07504204	T2	19950511	JP 1993-508846	19930930
ZA 9307286	A	19950630	ZA 1993-7286	19930930
HU 70482	A2	19951030	HU 1994-1631	19930930
AU 676491	B2	19970313	AU 1993-48311	19930930
US 5508310	A	19960416	US 1995-446080	19950519
US 5958980	A	19990928	US 1995-458911	19950602
US 6096786	A	20000801	US 1995-460207	19950602
US 5872151	A	19990216	US 1997-813915	19970307
PRAI GB 1992-20715	A	19921001		
GB 1992-26874	A	19921223		
US 1993-112849	B2	19930826		
US 1993-112992	B1	19930826		
EP 1993-307373	A3	19930917		
WO 1993-GB2039	W	19930930		
US 1994-224152	B1	19940407		
US 1995-462115	B1	19950605		

OS MARPAT 120:315820
AB The invention relates to the use of a class of compds. as immunopotentiators, compns. contg. such compds., their manuf., combinations of such compds. with anti-tumor or anti-infective drugs and the use of such combinations in the prophylaxis or treatment of diseases arising from tumors or infections. The compds. form a Schiff base or a hydrazone with T-cell surface carbonyl or amino groups for the potentiation of an immune response. Effects of 4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid on T-lymphocyte priming to antigen were demonstrated with mice.

L2 ANSWER 32 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 94166777 EMBASE
DN 1994166777
TI 31P MRS to monitor the induction of tumor hypoxia by the modification of the oxygen affinity of hemoglobin using BW 589C.
AU Kaira R.; Bremner J.C.M.; Wood P.J.; Sansom J.; Counsell C.J.R.; Stratford I.J.; Adams G.E.
CS Clinical Oncology Centre, Addenbrooke's NHS Trust, Box 193, Hills Rd.,Cambridge CB2 2QQ, United Kingdom
SO International Journal of Radiation Oncology Biology Physics, (1994) 29/2 (285-288).
ISSN: 0360-3016 CODEN: IOBPD3
CY United States
DT Journal; Conference Article
FS 014 Radiology
016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB Purpose: BW 589C induces severe tumor hypoxia by modifying the affinity of oxyhemoglobin, causing a left shift of the oxygen-hemoglobin dissociation curve. 31P magnetic resonance spectra (MRS) was used to monitor the effects of BW 589C on tumor energy metabolism in three experimental tumor models. Methods and Materials: HT-29 colon xenograft, murine transplantable RIF-1 fibrosarcoma and KHT sarcoma were studied in unanesthetised mice. 31P MR spectra were acquired on a 4.7 Tesla magnet before administering oral BW 589C (250 mg/kg) and after 3, 6, and 24 h.

Samples of tail vein blood were then taken for 2,3 DPG levels for RIF-1 and HT-29 tumors. Results: Doubling of inorganic phosphorus (P(i)) to total phosphorus was observed 5-6 h after BW 589C for all three tumor types. Although the left shift due to BW 589C persists at 24 h, the level of P(i) to total phosphorus returned to baseline with no significant difference from control values for the RIF-1 and HT-29 tumors. These results suggest that there was cellular metabolic adaptation to the reduction of oxygen delivery by BW 589C. This does not appear to involve 2,3 DPG as there was no significant alteration in tumor levels. The death of hypoxic cells may, also, have contributed to the recovery of P(i) to total phosphorus. Conclusion: The efficacy of bioreductive drugs can be enhanced by increasing the severity of tumor hypoxia. 31P MRS in conjunction with other techniques for assessing the intratumor environment could play an important role in planning cancer therapy.

L2 ANSWER 33 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 94166768 EMBASE
DN 1994166768
TI Bioreductive drugs for cancer therapy: The search for tumor specificity.
AU Adams G.E.; Stratford I.J.
CS MRC Radiobiology Unit,Didcot, Oxfordshire OX11 0RD, United Kingdom
SO International Journal of Radiation Oncology Biology Physics, (1994) 29/2 (231-238).
ISSN: 0360-3016 CODEN: IOBPD3
CY United States
DT Journal; Conference Article
FS 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The activity of three different classes of bioreductive drug, i.e., heterocyclic nitro compounds, N-oxides and quinones are compared. The major characteristics of RB-6145, tirapazamine and E09 are summarized and future directions for development of new bioreductive drugs are outlined. The concept of potentiating bioreductive drug activity by increasing tumor hypoxia is described and illustrated in particular by the use of photodynamic therapy (PDT) in combination with RSU-1069. Examples of how the therapeutic effectiveness of this approach can be studied by the use of 31P magnetic resonance spectroscopy is described. The effects of manipulation of nitric oxide (NO) levels in tumors by the use of modifiers of NO-synthase activity is illustrated by studies with the inhibitor nitro-L-arginine in experimental tumors. Associated changes in tumor physiology indicate promise for potential applications in therapy. Finally, changes in expression of reductase enzyme levels are considered in the context of the heterogenous nature of the tumor microenvironment.

L2 ANSWER 34 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 14
AN 93103384 EMBASE
DN 1993103384
TI The pharmacokinetics, tolerability and pharmacodynamics of ***tucaresol*** (589C80; 4[2-formyl-3-hydroxyphenoxymethyl]benzoic acid), a potential anti-sickling agent, following oral administration to healthy subjects.
AU Rolan P.E.; Parker J.E.; Gray S.J.; Weatherley B.C.; Ingram J.; Leavens W.; Wootton R.; Posner J.
CS Wellcome Research Laboratories, Langley Court,Beckenham, Kent BR3 3BS, United Kingdom
SO British Journal of Clinical Pharmacology, (1993) 35/4 (419-425).
ISSN: 0306-5251 CODEN: BCPHBM
CY United Kingdom
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB ***Tucaresol*** (589C80; 4[2-formyl-3-hydroxyphenoxymethyl] benzoic acid) interacts stoichiometrically with haemoglobin to increase oxygen affinity. By decreasing the proportion of insoluble deoxy sickle haemoglobin at capillary oxygen concentrations, ***tucaresol*** may be of therapeutic benefit in sickle cell anaemia. In this study, which involved the first administration to man, the pharmacokinetics and pharmacodynamics of ***tucaresol*** were studied in healthy male volunteers following oral doses of 200-3600 mg. Peak drug concentrations in plasma and erythrocytes were linearly related to dose; mean (s.d.) values were 95.8 (26.1) and 1035 (67) .mu.g ml-1, respectively, at the highest dose. Median t(max) in plasma was 6.5 h and in erythrocytes 24.5 h, when approximately 60% of the administered dose was in the target tissue. Plasma drug concentrations fell biexponentially with commencement of the apparent terminal elimination phase at approximately 24 h. The terminal elimination half-life from plasma increased with dose ($r = 0.77$; $P < 0.0001$) from 133-190 h at 400 mg to a mean (s.d.) of 289 (30) h at 3600 mg. Erythrocyte drug concentrations declined monoexponentially with a half-life that was always shorter than the apparent terminal half-life in plasma: overall mean (95% CI) of t(1/2) erythrocyte/t(1/2) plasma ratio was 0.57 (0.53, 0.61). The erythrocyte AUC/plasma AUC ratio increased with dose ($r = 0.67$; $P < 0.001$). The proportion of haemoglobin modified to a form with high oxygen affinity (% MOD) increased in a dose-related manner above doses of 800 mg reaching 19-26% after the 3600 mg dose. The %MOD was directly proportional to erythrocyte drug concentrations and declined in parallel during the elimination phase. The drug was well tolerated, with no clear effects on resting or exercise heart rates or blood pressures. Small increases in reticulocyte counts were seen following doses of 2800 and 3600 mg suggesting stimulation of erythropoiesis.

L2 ANSWER 35 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 92230320 EMBASE
DN 1992230320
TI Substituted benzaldehydes (12C79 and 589C80) that stabilize oxyhaemoglobin also protect sickle cells against calcium-mediated dehydration.
AU Stone P.C.W.; Nash G.B.; Stuart J.
CS Department of Haematology, Medical School, University of Birmingham,Birmingham B15 2TT, United Kingdom
SO British Journal of Haematology, (1992) 81/3 (419-423).
ISSN: 0007-1048 CODEN: BJHEAL
CY United Kingdom
DT Journal; Article
FS 025 Hematology
037 Drug Literature Index
LA English
SL English
AB Reversibly sickled cells from patients with homozygous sickle-cell disease were prepared by Percoll-Isopaque density gradient separation and subjected to 15 h of cyclical deoxygenation-reoxygenation in the presence of Ca. After 15 h the sickle cells became dehydrated, losing volume secondary to K efflux via the Ca-activated (Gardos) channel, and showed impaired filterability through 5 .mu.m diameter pores. The substituted benzaldehydes 12C79 and 589C80, which stabilize the oxy-conformation of sickle haemoglobin, showed an additional protective effect at pharmacological concentration by maintaining the K concentration, mean cell volume, and deformability of sickle cells. Drugs that increase the oxygen affinity of sickle haemoglobin may be more effective than specific inhibitors of Ca entry or K efflux in preserving the cation homeostasis and deformability of sickle cells during sickling in vivo.

L2 ANSWER 36 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 91070443 EMBASE
DN 1991070443
TI O2 levels in normal tissues.
AU Brewster A.E.; Moore J.L.
CS Department of Radiobiology, South Wales Regional Centre for Radiotherapy and Oncology, Cardiff CF4 7XL, United Kingdom
SO International Journal of Radiation Oncology Biology Physics, (1990) 19/6 (1628).
ISSN: 0360-3016 CODEN: IOBPD3
CY United States
DT Journal; Letter
FS 014 Radiology
016 Cancer
037 Drug Literature Index
LA English

L2 ANSWER 37 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 90274400 EMBASE
DN 1990274400
TI Rheological stress models for testing the effects of drugs on human erythrocytes.
AU Stuart J.
CS Department of Haematology, The Medical School, University of Birmingham, Birmingham B15 2TJ, United Kingdom
SO Revista Portuguesa de Hemoreologia, (1990) 3/2 (155-161).
ISSN: 0871-4649 CODEN: RPHEE5
CY Portugal
DT Journal; General Review
FS 025 Hematology
030 Pharmacology
037 Drug Literature Index
LA English

L2 ANSWER 38 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 89137250 EMBASE
DN 1989137250
TI Induction of severe tumor hypoxia by modifiers of the oxygen affinity of hemoglobin.
AU Adams G.E.; Stratford I.J.; Nethersell A.B.W.; White R.D.
CS MRC, Radiobiology Unit, Chilton, Didcot, Oxfordshire, OX11 ORD, United Kingdom
SO International Journal of Radiation Oncology Biology Physics, (1989) 16/5 (1179-1182).
ISSN: 0360-3016 CODEN: IOBPD3
CY United States
DT Journal
FS 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
023 Nuclear Medicine
LA English
SL English
AB Methods have been compared for inducing severe hypoxia in experimental tumors. Hypoxic fractions in the tumors were obtained from measurements of the displacement of cellular survival plots in vitro following tumor irradiation in vivo. Two compounds that displace to the left, oxygen-hemoglobin association curves greatly increase the hypoxic fractions in the tumors. The compound BW12C increases the hypoxic fractions in the KHT and Lewis-Lung tumors from about 10% to between 50-100%. The longer acting analogue BW589C increases hypoxic fraction in the KHT tumor to the same level achievable by treatment with the vaso-active drug hydralazine. The effect is also observed in the RIF-1 tumor even though the hypoxic fraction in this tumor is normally only about 1-3%. The kinetics for hypoxia induction by BW589C and its subsequent return to normal levels are comparable to those for the left-shifting of the oxy-hemoglobin association curve observable up to about 2 days post treatment.

L2 ANSWER 39 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 89227231 EMBASE
DN 1989227231
TI Modification of oxygen affinity in sickle cell anemia.
AU Johnson C.S.; Keidan A.J.; Sowter M.C.; White R.D.; Stuart J.
CS Department of Medicine, University of Southern California, Los Angeles, CA 90033, United States
SO Annals of the New York Academy of Sciences, (1989) 565/- (413-415).
ISSN: 0077-8923 CODEN: ANYAA
CY United States
DT Journal
FS 002 Physiology
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English

L2 ANSWER 40 OF 40 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 89104327 EMBASE
DN 1989104327
TI Pharmacological modification of oxygen affinity improves deformability of deoxygenated sickle erythrocytes: A possible therapeutic approach to sickle cell disease.
AU Keidan A.J.; Sowter M.C.; Johnson C.S.; Marwah S.S.; Stuart J.
CS Department of Haematology, Medical School, University of Birmingham, Birmingham B15 2TJ, United Kingdom
SO Clinical Science, (1989) 76/4 (357-362).

ISSN: 0143-5221 CODEN: CSCIAE
CY United Kingdom
DT Journal
FS 025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The formation of polymerized haemoglobin S in sickle cells is critically dependent on the concentration of deoxygenated haemoglobin so that compounds which increase the oxygen affinity of haemoglobin S are potential anti-sickling agents. BW12C [5-(2-formyl-3-hydroxyphenoxy)pentanoic acid] and BWA589C [4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid] are aromatic benzaldehydes that cause a dose-dependent left-shift of the oxygen saturation curve of haemoglobin S by stabilization of its oxy-(R)-conformation. A 5 .mu.m pore filtration method, which is highly sensitive to polymerization of haemoglobin S, was used to demonstrate a significant improvement in the deformability of deoxygenated sickle erythrocytes at concentrations (0.75-1.5 mmol/l) of BW12C and BWA589C that are achievable in vivo. Both compounds may therefore be of value for the treatment of sickle cell disease. Filtration of sickle cells through pores of 5 .mu.m diameter is a sensitive technique for evaluating the rheological effects of potential anti-sickling compounds.

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FULL ESTIMATED COST 89.34 89.49

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CA SUBSCRIBER PRICE -4.12 -4.12

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Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s tucaresol
L3 1 TUCARESOL

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 84290-27-7 REGISTRY
CN Benzoic acid, 4-[(2-formyl-3-hydroxyphenoxy)methyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 589C
CN 589C80
CN BWA 589C
CN ***Tucaresol***
FS 3D CONCORD
MF C15 H12 O5
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CEN, CIN, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, TOXCENTER, TOXLIT, USAN, USPATFULL
Other Sources: WHO

/ Structure 1 in file .gra /

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19 REFERENCES IN FILE CA (1967 TO DATE)
19 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> FIL EMBASE BIOSIS CAPLUS
COST IN U.S. DOLLARS SINCE FILE TOTAL
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FULL ESTIMATED COST 5.92 95.41

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=> s Benzoic acid, 4-[(2-formyl-3-hydroxyphenoxy)methyl]
MISSING OPERATOR '4-[(2-FORMYL-3'
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=> s l1 and vaccin?
L4 3 L1 AND VACCIN?

=> dup rem l
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4 IS NOT VALID HERE
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=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 3 DUP REM L4 (0 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 2000:161160 CAPLUS
DN 132:199039
TI Method of DNA ***vaccination***
IN Charo, Jehad; Kiessling, Rolf
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000012121	A1	20000309	WO 1999-EP6217	19990825

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9957402	A1	20000321	AU 1999-57402	19990825
EP 1107785	A1	20010620	EP 1999-944505	19990825

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

NO 2001000922	A	20010423	NO 2001-922	20010223
PRAI GB 1998-18627	A	19980826		
WO 1999-EP6217	W	19990825		

AB A method of ***vaccinating*** a mammal against a disease state, comprising administrating to said mammal, within an appropriate vector, a nucleotide sequence encoding an antigenic peptide assocd. with the disease state; addnl. administering to said mammal a compd. which enhances both humoral and cellular immune responses initiated by the antigenic peptide, the compd. being selected from the list contained herein, wherein the compd. is preferably ***Tucaresol*** or a physiol. acceptable salt or ester thereof, where appropriate.
RE.CNT 5
RE
(1) Rhodes, J; IMMUNOLOGY TODAY 1996, V17(9), P436 CAPLUS
(2) Rhodes, J; NATURE 1995
(3) Sasaki, S; CLINICAL AND EXPERIMENTAL IMMUNOLOGY 1998, V111, P30 CAPLUS
(4) Sasaki, S; INFECTION AND IMMUNITY 1998, V66(2), P823 CAPLUS
(5) Wellcome Found; WO 9407479 A 1994 CAPLUS

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 2000:891632 CAPLUS
DN 134:41090
TI Peptide immunogen as ***vaccine*** for allergic reaction and its preparation
IN Liu, Qingliang
PA Shanghai Inst. of Biological Products, Ministry of Health, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 30 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1253953	A	20000524	CN 1998-121989	19981112

AB Human IgE receptor-binding peptide epitopes are disclosed for use as ***vaccines*** for treating hypersensitivity. The peptides are conjugated with carrier protein, or are fusion protein contg. carrier protein, and are administered with adjuvant. The carrier protein is selected from hepatitis B surface antigen, hepatitis B core antigen, or nucleoprotein of rabies virus, preferably hepatitis B surface antigen. The adjuvant is liposome, Al(OH)3 gel, gamma-inulin, or ***tucaresol*** , preferably liposome. The human ***vaccine*** is prepd. by synthesizing and purifying peptide immunogen, conjugated with carrier protein in the presence of chem. crosslinking agent (or transferring into E. coli, saccharomyces, or phage, expressing, sepg.), and mixing with adjuvant. The chem. crosslinking agent is glutaraldehyde, bis(diazo)benzidine, etc.

L5 ANSWER 3 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001082191 EMBASE
TI Overview of HBV therapy.
AU Pessoa M.G.; Wright T.L.
CS M.G. Pessoa, Dept. of Vet. Affairs Med. Center, 4150 Clement Street, San Francisco, CA 94121, United States
SO Advances in Experimental Medicine and Biology, (1999) 458/- (1-10).
Refs: 31
ISSN: 0065-2598 CODEN: AEMBAP
CY United States
DT Journal; Conference Article
FS 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English

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COST IN U.S. DOLLARS SINCE FILE TOTAL
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FULL ESTIMATED COST 11.11 106.52

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NEWS 6 Apr 23 PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
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NEWS 8 Jun 20 Published patent applications (A1) are now in USPATFULL
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NEWS 14 Oct 09 Korean abstracts now included in Derwent World Patents Index
NEWS 15 Oct 09 Number of Derwent World Patents Index updates increased
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NEWS 18 Oct 22 DGENE GETSIM has been improved
NEWS 19 Oct 29 AAASD no longer available
NEWS 20 Nov 19 New Search Capabilities USPATFULL and USPAT2
NEWS 21 Nov 19 TOXCENTER(SM) - new toxicology file now available on STN
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NEWS 23 Nov 29 DWPI revisions to NTIS and US Provisional Numbers
NEWS 24 Nov 30 Files VETU and VETB to have open access
NEWS 25 Dec 10 WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
NEWS 26 Dec 10 DGENE BLAST Homology Search
NEWS 27 Dec 17 WELDASEARCH now available on STN
NEWS 28 Dec 17 STANDARDS now available on STN
NEWS 29 Dec 17 New fields for DPCI
NEWS 30 Dec 19 CAS Roles modified
NEWS 31 Dec 19 1907-1946 data and page images added to CA and CAplus

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DICTIONARY FILE UPDATES: 18 DEC 2001 HIGHEST RN 376576-00-0

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http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s tucaresol
L1 1 TUCARESOL

=> FIL EMBASE BIOSIS CAPLUS
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FULL ESTIMATED COST 4.11 4.26

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L2 60 L1

=> s l2 and vaccin?
L3 3 L2 AND VACCIN?

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 3 DUP REM L3 (0 DUPLICATES REMOVED)

=> s l2 and immunopotentiat?
L5 13 L2 AND IMMUNOPOTENTIAT?

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6 8 DUP REM L5 (5 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:262548 BIOSIS
DN PREV200100262548
TI Schiff base-forming compounds inhibit estrogen receptor-positive and -negative mammary carcinoma cell proliferation.
AU Davis, Barbara A. (1)
CS (1) Molecular Nutrition Laboratory, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061 USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A963. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Vitamin B6, in the form of pyridoxal (PL), inhibits growth of both estrogen receptor-positive (ER+) and -negative (ER-) mammary carcinoma cells in vitro. In the experiments described here, Tucaresol (TUC), a Schiff base-forming benzaldehyde, was used along side PL to compare the growth inhibitory properties of these two compounds. T-47D (ER+) and MDA-MB-231 (ER-) cells were cultured in phenol red-free medium plus vehicle control, 100 muM TUC, 300 muM TUC, 100 muM PL or 300 muM PL for 3d. At the 100 muM dose, TUC and PL inhibited (3H)-thymidine incorporation into DNA of cells similarly (52 and 58.6% of control cells, respectively). However at the 300 muM dose, TUC was more potent than PL, inhibiting (3H)-thymidine incorporation to 3% vs. 23% of control cells, respectively. TUC is an orally bioavailable, systemic ***immunopotentiating*** drug known to form a Schiff base with amines on the surface of T helper lymphocytes. It has been shown to inhibit colon adenocarcinoma and melanoma growth in vivo, presumably via its ***immunopotentiating*** properties. Data presented here suggest that TUC may inhibit cancer cell growth by a more direct mechanism, since only mammary carcinoma cells were present in our culture system. Further study of the Schiff base-forming compounds, vitamin B6 and TUC, will enhance our understanding of the mechanism by which they inhibit mammary carcinoma cell growth and may lead to identification of novel therapeutic agents.

L6 ANSWER 2 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001362418 EMBASE
TI Schiff base-mediated co-stimulation primes the T-cell-receptor-dependent

calcium signalling pathway in CD4 T cells.
AU Hall S.R.; Rhodes J.
CS Dr. S.R. Hall, Building 6, GlaxoSmithKline Res. and Development, Medicines Research Centre, Stevenage SG1 2NY, United Kingdom. srh18219@gsk.com
SO Immunology, (2001) 104/1 (50-57).
Refs: 27
ISSN: 0019-2805 CODEN: IMMUAM
CY United Kingdom
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB In addition to macromolecular interactions that provide co-stimulation during antigen-presenting cell (APC) and CD4(+) T-cell conjugation, covalent chemical events between specialized ligands have been implicated in T-cell co-stimulation. These take the form of transient Schiff base formation between carbonyls and amines expressed on APC and T-cell surfaces. Small Schiff base-forming molecules, such as tucaresol, can substitute for the physiological donor of carbonyl groups and provide co-stimulation to T cells, thereby functioning as orally active ***immunopotentiatory*** drugs. The Schiff base co-stimulatory pathway in T cells has been partially characterized in terms of changes in Na(+) and K(+) transport, and activation of the mitogen activated protein kinase (MAPK) ERK2. In the present study, the effects of Schiff base co-stimulation by tucaresol on the T-cell receptor (TCR)-dependent pathway leading to Ca(2+) release were investigated. Schiff base co-stimulation by tucaresol was found to prime for enhanced TCR-dependent phospholipase C-gamma. phosphorylation, inositol 1,4,5-triphosphate production, and Ca(2+) mobilization that correlated with functional enhancement of interleukin-2 production in primary T cells. The effects on Ca(2+) occurred comparably in Jurkat and primary CD4(+) T cells responding to anti-CD3 monoclonal antibody. Enhancement of the Ca(2+) response required a 10-min priming period and was prevented by prior covalent ligation of cell-surface free amino groups by sulpho-N-hydroxy succinimido-biotin; clofilium-mediated inhibition of tucaresol-induced changes in intracellular K(+); and selective inhibition of the MAPK pathway. The data are consistent with a priming mechanism in which late co-stimulation-triggered events exert a positive influence on early TCR-triggered events. In additional studies of murine T cells expressing trans-gene TCRs, tucaresol was likewise shown to prime for enhanced Ca(2+) mobilization in response to physiological TCR-engagement by MHC-peptide complexes.

L6 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:232894 BIOSIS
DN PREV199799532097
TI A novel ***immunopotentiating*** agent, tucaresol: Results from a multicenter, pilot study in patients with metastatic melanoma.
AU Kirkwood, J. M. (1); Schuchter, L. M.; Donnelly, S.; Stover, L.; Whiteside, T. L.; Burnham, J. P.; Heitman, C. K.; Johnston, J. M.
CS (1) Univ. Pittsburgh Cancer Inst., Pittsburgh, PA 15213 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 402.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.
DT Conference; Abstract
LA English

L6 ANSWER 4 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AN 97214933 EMBASE
DN 1997214933
TI Potentiation of the immune system by Schiff base-forming drugs. Mechanism of action and therapeutic potential.
AU Chen H.; Hall S.; Zheng B.; Rhodes J.
CS Dr. J. Rhodes, Immunology Unit, Cellular Sciences Division, Glaxo Wellcome Research/Development, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom
SO BioDrugs, (1997) 7/3 (217-231).
Refs: 68
ISSN: 1173-8804 CODEN: BIDRF4
CY New Zealand
DT Journal; General Review
FS 002 Physiology
004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB CD4+ T lymphocytes, which orchestrate immune responses, receive a cognitive signal when clonally distributed receptors are occupied by peptides bound to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. The latter cells provide costimulatory or accessory signals through macromolecules such as B7.1 and B7.2, which interact with coreceptors on T cells to regulate outcomes in terms of T cell activation or specific nonresponsiveness. Complementary studies of the interactions between antigen-presenting cells and T helper cells at the chemical level have implicated Schiff base formation between specialised carbonyls and amines, constitutively expressed on the surfaces of antigen-presenting cells and T cells, as an essential element in specific T cell activation. Small Schiff base-forming molecules can substitute for the natural donor of carbonyl groups and provide a costimulatory signal to the T cell. From this class of Schiff base-forming costimulatory molecules, the small xenobiotic substituted benzaldehyde, tucaresol, has been selected for development and testing as an ***immunopotentiatory*** drug. Tucaresol, which is orally bioavailable and systemically active, enhances CD4+ T helper cell and CD8+ cytotoxic T cell responses in vivo, and selectively favours a T helper 1 profile of cytokine production. In murine models of virus infection and syngeneic tumour growth it has substantial therapeutic activity. Schiff base formation by tucaresol on T cell surface amines provides a costimulatory signal to the T cell through a mechanism that activates clofilium-sensitive K+ and Na+ transport. The pathway utilised by tucaresol converges with T cell receptor signalling at the level of mitogen-activated protein (MAP) kinase, promoting the activation of MAP kinase kinase (MEK) and consequential tyrosyl phosphorylation of ERK2. Tucaresol is the first orally active, mechanism-based ***immunopotentiatory*** drug available for therapeutic testing. It is currently undergoing phase I/II clinical trials in chronic hepatitis B virus infection, HIV infection and malignant melanoma.

L6 ANSWER 5 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN 96284595 EMBASE
DN 1996284595
TI Schiff base forming drugs: Mechanisms of immune potentiation and therapeutic potential.
AU Chen H.; Rhodes J.
CS Immunology Unit, Medicine Research Centre, Glaxo Wellcome Research/Development, Gunnels Wood Road,Stevenage, Hertfordshire SG1 2NY, United Kingdom
SO Journal of Molecular Medicine, (1996) 74/9 (497-504).
ISSN: 0946-2716 CODEN: JMLME8
CY Germany
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB CD4 T-lymphocytes, which orchestrate immune responses, receive a cognitive signal when clonally distributed receptors are occupied by MHC class II bound peptides on antigen-presenting cells. The latter provide costimulatory or accessory signals through macromolecules such as B7.1 and B7.2 which interact with coreceptors on T-cells to regulate outcomes in terms of T-cell activation or specific non-responsiveness. Complementary studies at the chemical level have implicated Schiff base formation between specialised carbonyls and amines, constitutively expressed on antigen-presenting cell and T-cell surfaces, as an essential element in specific T-cell activation. The small xenobiotic Schiff base forming molecule tucaresol, which substitutes for the physiological donor of carbonyl groups to provide a costimulatory signal to CD4 T-helper lymphocytes (Th-cells), has been developed for testing as an ***immunopotentiatory*** drug. Tucaresol, which is orally bioavailable and systemically active, enhances CD4 Th-cell and CD8 cytotoxic T-cell responses in vivo and selectively favours a Th1-type profile of cytokine production. In murine models of virus infection and syngeneic tumour growth it has substantial therapeutic activity. Schiff base formation by tucaresol on T-cell surface amines provides a costimulatory signal to the T-cell through a mechanism that activates clofilium-sensitive K+ and Na+ transport. The signalling pathway utilised by tucaresol converges with T-cell receptor signalling at the level of MAP kinase, promoting the tyrosyl phosphorylation of ERK2 by MEK (mitogen-activated protein kinase kinase). The Schiff base forming class of ***immunopotentiatory*** drug provides the first orally active, mechanism-based ***immunopotentiatory*** agents for therapeutic testing. Tucaresol is currently undergoing pilot phase I/II clinical trials as an ***immunopotentiator*** in chronic hepatitis B virus infection, HIV infection and malignant melanoma.

L6 ANSWER 6 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
AN 96256778 EMBASE
DN 1996256778
TI Covalent chemical events in immune induction: Fundamental and therapeutic aspects.
AU Rhodes J.
CS Immunology Unit, Division of Cellular Sciences, Glaxo Wellcome Medicines Res. Centre, Gunnels Wood Road,Stevenage, Hertfordshire SG1 2NY, United Kingdom
SO Immunology Today, (1996) 17/9 (436-441).
ISSN: 0167-5699 CODEN: IMTOD8
CY United Kingdom
DT Journal; General Review
FS 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Costimulatory macromolecules on antigen-presenting cells and T cells play a critical regulatory role in immune induction and thus make useful immunotherapeutic targets. However, as reviewed here, by John Rhodes, studies of complementary chemical events are beginning to reveal a new level of intercellular and intracellular signalling that can be targeted by small, orally active therapeutic agents. One such molecule, tucaresol, is being developed for testing as a systemic ***immunopotentiatory*** drug.

L6 ANSWER 7 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
AN 96077383 EMBASE
DN 1996077383
TI Therapeutic potential of Schiff base-forming drugs.
AU Rhodes J.
CS Immunology Unit, Research Division, Glaxo Wellcome Research/Development,Beckenham, Kent, United Kingdom
SO Expert Opinion on Investigational Drugs, (1996) 5/3 (257-268).
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Despite the sustained efforts of immunologists, drugs with which to potentiate the immune system in chronic infectious disease and cancer have remained elusive. CD4+ T helper lymphocytes, activated by antigens bound to MHC class II molecules on specialised antigen presenting cells (APCs), are an important target in any ***immunopotentiatory*** strategy because they orchestrate immune responses. In addition to presenting antigen, APCs also express surface macromolecules that provide essential co-stimulatory signals through interactions with co-receptors on T-cells. As a consequence of some of these macromolecular interactions, transient covalent chemical events occur between specialised carbonyl and amino groups to form reversible Schiff bases and this process is essential for optimal immune induction. This chemical event can be mimicked by small Schiff base-forming molecules that substitute for the natural donor of carbonyl groups and directly co-stimulate T-cells, providing a class of low-molecular weight agents that potently enhance the induction of immune responses in vivo. One such molecule, tucaresol (Glare Wellcome), has been developed for testing as an orally bioavailable, systemically active ***immunopotentiator*** drug. The formation of a Schiff base by

tucaresol on specialised T-cell surface amines provides a co-stimulatory signal to the T-cell through a mechanism that activates Na+ and K+ transport. The signalling pathway initiated by tucaresol converges with T-cell receptor signalling at the level of tyrosyl phosphorylation of the MAP kinase ERK2. Tucaresol co-stimulation preferentially favours a Th1-type profile of cytokine production, enhancing the release of interleukin (IL)-2 and interferon-.gamma. (IFN.gamma.), but not IL-4 or IL-6. This may be therapeutically favourable in promoting immune responses to intracellular pathogens, such as viruses, mycobacteria and protozoal parasites, as well as responses to immunogenic tumours. The Schiff base-forming class of ***immunopotentiatory*** drug provides the first orally-active, mechanism-based ***immunopotentiatory*** agent for therapeutic testing. Tucaresol is currently undergoing pilot Phase I/II clinical trials as an ***immunopotentiator*** in chronic hepatitis B virus infection, HIV infection and malignant melanoma.

L6 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS
AN 1994:315820 CAPLUS
DN 120:315820
TI ***Immunopotentiatory*** agents
IN Rhodes, John Richard
PA The Wellcome Foundation Ltd., UK
SO PCT Int. Appl., RCPP
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9407479	A2	19940414	WO 1993-GB2039	19930930
	WO 9407479	A3	19940721		
	W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	EP 609606	A1	19940810	EP 1993-307373	19930917
	EP 609606	B1	19961211		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	EP 678298	A2	19951025	EP 1995-110267	19930917
	EP 678298	A3	19960529		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	AT 146075	E	19961215	AT 1993-307373	19930917
	ES 2096215	T3	19970301	ES 1993-307373	19930917
	CN 1091005	A	19940824	CN 1993-114444	19930930
	EP 614357	A1	19940914	EP 1993-921034	19930930
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07002660	A2	19950106	JP 1993-277300	19930930
	JP 07504204	T2	19950511	JP 1993-508846	19930930
	ZA 9307286	A	19950630	ZA 1993-7286	19930930
	HU 70482	A2	19951030	HU 1994-1631	19930930
	AU 676491	B2	19970313	AU 1993-48311	19930930
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PRAI	GB 1992-20715	A	19921001		
	GB 1992-26874	A	19921223		
	US 1993-112849	B2	19930826		
	US 1993-112992	B1	19930826		
	EP 1993-307373	A3	19930917		
	WO 1993-GB2039	W	19930930		
	US 1994-224152	B1	19940407		
	US 1995-462115	B1	19950605		

OS MARPAT 120:315820
AB The invention relates to the use of a class of compds. as ***immunopotentiators*** , compns. contg. such compds., their manuf., combinations of such compds. with anti-tumor or anti-infective drugs and the use of such combinations in the prophylaxis or treatment of diseases arising from tumors or infections. The compds. form a Schiff base or a hydrazone with T-cell surface carbonyl or amino groups for the potentiation of an immune response. Effects of 4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid on T-lymphocyte priming to antigen were demonstrated with mice.

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—Logging off of STN—

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		27.64	31.90

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	ENTRY	SINCE FILE SESSION	TOTAL
CA SUBSCRIBER PRICE		-0.59	-0.59

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